A far downstream enhancer for murine Bcl11b controls its T-cell specific expression.

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Public Summary:

Scientific Abstract:
Bcl11b is a T-cell specific gene in hematopoiesis which begins expression during T- lineage commitment and is required for this process. Aberrant expression of BCL11b or proto-oncogene translocation to the vicinity of BCL11B can be a contributing factor in human T-ALL. To identify the mechanism that controls its distinctive T-lineage expression, we corrected the identified Bcl11b transcription start site and mapped a cell-type-specific differentially methylated region bracketing the Bcl11b promoter. We identified a 1.9-kb region 850 kb downstream of Bcl11b, "Major Peak", distinguished by its dynamic histone marking pattern in development that mirrors the pattern at the Bcl11b promoter. Looping interactions between promoter-proximal elements including the differentially methylated region and downstream elements in the Major Peak are required to recapitulate the T-cell specific expression of Bcl11b in stable reporter assays. Functional dissection of the Major Peak sequence revealed distinct subregions, in which TCF-1 sites and a conserved element were required for T lineage-specific activation and silencing in non-T cells. A BAC encompassing the full Bcl11b gene still required addition of the Major Peak to exhibit T-cell specific expression. Thus, promoter-proximal and Major Peak sequences are cis-regulatory elements that interact over 850 kb to control expression of Bcl11b in hematopoietic cells.